PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X-15968	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US 03/25860	International filing date *(day/month/year)* 12.09.2003	Priority date *(day/month/year)* 18.09.2002
International Patent Classification (IPC) or both national classification and IPC C07D215/00		
Applicant ELI LILLY AND COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03.03.2004	26.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer Hoepfner, W Telephone No. +49 30 25901-337

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/25860

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-70 as originally filed

Claims, Numbers

1-14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 9-14 (with respect to industrial applicability)

   because:

   ☒ the said international application, or the said claims Nos. 9-14 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-14
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-8
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 9-14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, the International Examination Authority fully concurs with the objection put forward by the International Search Authority and no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV

Lack of unity of invention

The document D1 (see Re Item V below) discloses certain (dihydro)indoles of formula (I) and their medical use. A part of these compounds of the said formula (I) has in common the same structural features as the compounds of formula (I) of the present claim 1, namely a (dihydro) indole having N-alkylcarbonyl substitution and having a second N-containing heterocycle which is linked to the benzene moiety by means of an N-alkyloxy group. Moreover, in the worked Examples of D1, there is given clear preference to these particular embodiments.

Consequently, with this overlap of common structural features, it is no longer possible to define one single distinguishing feature between the subject-matter of the present claim 1 and the subject-matter of D1.

However, withe the presence of more than one different distinguishing feature and with the umbrella of any common distinguishing structural feature being lost, the subject-matter of the present claim 1 can no longer be regarded as being unitarian and is therefore split into 6 different inventions (non-unity a posteriori), the said inventions being as follows:

- provision of a compound of formula (I) based on (dihydro)indole with X=H and its medical use (invention #1);
- provision of a group of compounds of formula (I) based on (dihydro)indole with X=-COR^3 and its medical use (invention #2);
- provision of a compound of formula (I) based on (dihydro)indole with X=-CH_2R^4 and its medical use (invention #3);

- provision of a compound of formula (I) based on (dihydro)indole with X=-SO_2R^5 and its medical use (invention #4);
- provision of a compound of formula (I) based on dihydroquinolin(on)e or tetrahydroquinoline and its medical use (invention #5); and
- provision of a compound of formula (I) based on indolone and its medical use (invention #6).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; *citations and explanations supporting such statement*

Reference is made to the following documents:

D1: WO-A-0214273
D2: WO-A-0244141
D3: WO-A-0168652

Novelty

The document D1 discloses indoline derivatives and their use as medicaments for the treatment of cognitive disorders and feeding disorders. The compounds of D1 differ from the compounds of the present claim 1 in that the linking group between the nitrogen atom of the heterocyclic moiety and the aromatic group is based on acroleine (see page 1, line 5; page 1, formula (I); page 9, lines 12-14; page 35, Table 1; page 40, Table 3).

The document D2 discloses H_3 antagonists and their use as medicaments for the treatment of CNS-hyperactivity and obesity. The compounds of D2 are based on diphenylmethane and imidazole, which are linked to each other by means of a heterocycloalkyl linking group . In the worked Examples of D2 this linking group consists of different 1,4-bis-alkyl piperazines (see page 1, line 6; page 8, lines 5, 6; page 8, formula I; page 15, lines 22, 23; Page 52, Table 1).

Lastly, the document D3 discloses H_3 antagonists and their use as medicaments suitable for the reduction of weight. The compounds of D3 are based on condensed imidazoles such as tetrahydrobenzimidazole (see page 1, line 8; page 2, lines 19, 20; page 6, formula (I); page 33, line 2; Examples).

In view of these documents, novelty has to be acknowledged for the subject-matter of the independent claims 1, 8, 9, 12 and 14 and the dependent claims 2-7, 10, 11 and 13.

Inventive step

The document D1 is regarded as the closest prior art for the novel subject-matter, since it addresses a similar problem, namely the provision of compounds useful for the treatment of cognitive and feeding disorders; and since its compounds come structurally closest to the compounds of claim 1.

As outlined under Re Item IV above, the novel subject-matter consists of 6 different inventions. The distinguishing features between these 6 inventions and D1 are as follows:

- provision of a compound of formula (I) based on (dihydro)indole with X=H (invention #1);
- provision of a group of compounds of formula (I) based on (dihydro)indole with X=-COR^3 (invention #2);
  - provision of a compound, wherein R^3 has the meaning -(C_1-C_8) alkyl (sub-invention #2.1);
  - provision of a compound, wherein R^3 has the meaning -(C_3-C_8) cycloalkyl (sub-invention #2.2);
  - provision of a compound, wherein R^3 has the meaning -O(C_1-C_8) alkyl (sub-invention #2.3);
  - provision of a compound, wherein R^3 has the meaning 2-pyrrolidinyl (sub-invention #2.4);
  - provision of a compound, wherein R^3 has the meaning furanyl or thienyl (sub-invention #2.5);
  - provision of a compound, wherein R^3 has the meaning -NH- (sub-invention #2.6);
  - provision of a compound, wherein R^3 has the meaning -CH2- (sub-invention #2.7);
- provision of a compound of formula (I) based on (dihydro)indole with X=-CH_2R^4 (invention #3);
- provision of a compound of formula (I) based on (dihydro)indole with X=-SO_2R^5 (invention #4);
- provision of a compound of formula (I) based on dihydroquinolin(on)e or tetrahydroquinoline (invention #5); and
- provision of a compound of formula (I) based on indolone (invention #6).

In the absence of any evidence for an unexpected technical effect linked to one of these features, in each case the objective problem solved by the respective subject-matter can merely be seen as the provision of further compounds useful for the treatment of cognitive and feeding disorders.

The claimed solutions to this very general problem underlying the 6 inventions consist of the selection of those compounds from the generic formula (I) of D1 wherein R^5 has the meaning "N-linked heterocycle" in combination with a specific modification of this selection, namely

- removal of any substituent at the heterocyclic nitrogen atom of D1 (X=H; invention #1);
- replacement of the unsaturated alkyl at the carbonylic carbon atom of D1 with certain groups R^3 (invention #2);
- replacement of the whole substituent at the heterocyclic nitrogen atom of D1 with X=-CH_2R^4 (invention #3);
- replacement of the whole substituent at the heterocyclic nitrogen atom of D1 with X=-SO_2R^5 (invention #4);
- replacement of the (dihydro)indole of D1 with dihydroquinolin(on)e or tetrahydroquinoline (invention #5); and
- replacement of the (dihydro)indole of D1 with dihydroindolone (invention #6).

However, since none of these solutions was suggested by the prior art neither alone nor in combination, the presence of inventive activity could be acknowledged for each of these independent solutions, even in the absence of an unexpected technical effect.

Formal matters

According to the worked Examples on file, there is given clear preference to compounds of formula (I) with Y=3-piperidin-1-yl-propoxy, which should have been made the subject of the main claim.

Industrial applicability

There is no doubt that the subject-matter of the present claims 1-8 is industrially applicable.

However, for the assessment of the present claims 9-14 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.